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Evaluation of leptin and lipid profile parameters in patients of T2DM in a tertiary care center of the Kumaun region of Uttarakhand

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ABSTRACT

Introduction: In India, T2DM is a major health problem due to its rising prevalence and associated complications. The role and mechanism of leptin and insulin in the etiopathogenesis of type 2 diabetes mellitus have been studied and reviewed in varying ethnic populations. However in the Kumaun region of Uttarakhand studies regarding the association of leptin and insulin in type 2 diabetes are lacking, for this the present study was conducted.
Materials and Methods : A total of 100 subjects, including fifty known T2DM patients and fifty healthy Age, Gender [Manish1] and BMI matched controls were[Manish2] enrolled in this cross-sectional study. Anthropometric and biochemical parameters including leptin, insulin, fasting glucose, HbA1c, and lipid profile were estimated in all the subjects by standard protocols.
Results: Higher leptin levels ($p< 0.001$) were observed in diabetic cases as compared to healthy controls. A significant and positive correlation of leptin was observed with HOMA IR ($r=0.346$, $p<0.001$), waist circumference ($r=0,482$, $p<0.01$), and dyslipidemias in diabetic subjects. However, a better and strong correlation was observed in diabetic cases as compared to healthy controls.
Conclusions: High leptin levels are associated with insulin resistance and dyslipidemia in diabetic cases in this region.

1. Introduction

Type 2 diabetes mellitus, characterized by chronic hyperglycemia may result from multiple factors including genetic predisposition, dietary transitions, lifestyle changes, and environmental factors.[1] Despite improvements in healthcare facilities, treatment, and diagnostic techniques the prevalence of T2DM is increasing worldwide.[2] According to International Diabetes Federation, 415 million people across the world are diabetics and this number will reach 642 million by 2040.[3] In India, the State-Level Disease Burden Initiative Diabetes study collaborators have projected that by 2025 the number of cases of diabetes would be 69.9 million with a vast majority still undiagnosed.[4]

Leptin (derived from the greek word lepto's meaning thin's) is one of the adipocyte-derived hormones (adipokine).[5] Under normal physiological conditions, leptin plays a pivotal role in energy homeostasis, metabolic pathways regulation, and insulin action.[5,6] It decreases food intake (anorexigenic), increases energy expenditure, and partitions calorie surplus.[7] These effects of leptin are mediated by leptin receptors on neurons in the mediobasal arcuate nucleus of the hypothalamus[8] and organs such as the heart, liver, kidneys, pancreas, bone, and others.[9,10]

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Leptin modulates the function of β-cells in the pancreas by increasing peripheral tissue's responsiveness to insulin and affects energetic metabolism.[10] In hepatic tissue, leptin regulates glucose and lipid metabolism as well as homeostasis.[11,12] In other peripheral tissues, leptin may stimulate inflammatory reactions, oxidative stress, atherogenesis, and thrombosis which have implicated endothelial dysfunction, arterial stiffness, and the development of atherosclerotic plaques.[12] Resistance to leptin action or its deficiency is involved in the etiopathogenesis of obesity, atherosclerosis, hypertension, coronary artery disease, metabolic syndrome, gestational diabetes, preeclampsia, and type 2 diabetes mellitus.[13–15]

Studies conducted globally as well as in India, regarding leptin levels concerning diabetes have shown inconsistent results. Some studies show higher leptin levels in diabetic populations than controls,[16] while others showed lower levels of leptin in diabetics[17] and still, others observed no difference.[18] This controversial data may be attributed to patient selection criteria or due to the effect of anti-diabetic drugs, insulin resistance, and ethnic or geographical variations. To our knowledge, no data has been reported in the Kumaun

2. Aims and Objectives

1. To evaluate the levels of serum leptin, insulin, and Some lipid profile parameters in T2DM patients and healthy controls.
2. To study if there is a correlation between serum leptin levels and insulin resistance in the study population.

3. Material and Methods

This was a crossectional study carried out in the Department of Biochemistry and Medicine, Government Medical College Haldwani.

3.1. Study subjects

100 subjects were enrolled in this study, out ofhistory of patients taking antidiabetic therapy or according to the classification of the ADAas havingng plasma glucose levels >, cancer, Controls were Fifty age, gender, and apparently, BMI-matched individuals. These were the relatives accompanying other patients attending medicine OPD for some minor illnesses. All controls were not taking any medication from last year and had no family history of diabetes mellitus. The subjects with endocrine disease, renal or hepatic diseases, and those receiving medications that control glucose metabolism, hypertension, or hyperlipidemia were excluded from the study.

3.2. Sample collection

Taking all the aseptic precautions a venous blood sample (6 mL) was collected from all the study subjects in fasting state. The sample was divided into two aliquots. The one 3 ml for biochemical analysis was distributed in a fluoride-containing vial for detecting fasting blood glucose, an EDTA vial for HbA1c analysis, and in a plain tube for estimation of other biochemical parameters.

For estimation of Insulin and leptin, the rest 3 mL of blood was transferred in plain vials and centrifuged for separation of serum. Serum was immediately transferred in Eppendorf vials which were stored at -80 °C, till further analysis.

3.3. Anthropometric assessment

Of all the T2DM patients and healthy controls weight and height were measured according to standard protocol.[19] BMI was calculated by software with the formula: BMI (kg/m2) = Weight (kg)/ Height (m2).

Waist circumference was measured at midway between the costal margin and the iliac crest. Hip circumference was taken as the largest circumference at the posterior extension of the buttocks.

Waist-to-hip ratio (WHR) was also calculated as waist circumference divided by hip circumference.

3.4. Biochemical analysis

Samples collected from study groups were processed and analyzed on Cobas 501c Roche manufactured, fully automated biochemistry analyzer in the Biochemistry central laboratory.

Lab investigations done were those of fasting blood glucose, glycosylated hemoglobin (HbA1c), lipid profile including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C). All estimations were performed on the closed system using the manufacturer's kit. The normal range of measured parameters was as follows: fasting blood glucose =70- 100 mg/dL; HbA1c < 6.5%; total cholesterol < 200 mg/dL; TG < 170 mg/dL; LDL-C = 90-130 mg/dL; HDL-C ≥ 40 mg/dL in Males and ≥ 50 mg/dL in Females.

Fasting serum insulin levels (μIU/mL) were measured in a fully automatic immunoassay analyzer, E 411 of ROCHE based on the principle chemiluminescent immunoassay (CLIA) technique. Samples were quantitatively analyzed within a few hours of sample collection following the package-insert instructions. Insulin levels of 2-25 μIU/mL were considered to be normal.

Homeostatic model assessment-insulin resistance (HOMA-IR) was used to evaluate insulin resistance (IR). It was calculated by software using the formula:

HOMA IR= Fasting serum insulin (IU/mL) X Fasting plasma glucose (mg/dL)/405

For the classification of IR, the HOMA score was used as a reference: 0.5-1 optimally suggesting insulin sensitivity, 1-1.9 for early IR, 1.9 - 2.9 for low IR, and> 2.9 for significant IR.[20]

Serum leptin levels were estimated by sandwich ELISA using DBC Diagnostics Biochem, Canada Inc. kits, as per the manufacturer's instructions. The normal range taken for serum leptin was 3.7 - 11.1 ng/mL for females while 2.0 - 5.6 ng/mL for males for all age groups.

3.5. Statistical analysis

Data were analyzed using a statistical package for social sciences software package version 20 (IBM SPSS, Chicago, Illinois, USA). The data were expressed as mean ± SD for continuous variables. Student t-test detected the difference in two variables of measured parameters. The Spearman correlation coefficient determined the correlation between serum leptin and demographic and biochemical parameters.

The results were considered nonsignificant if the P value was > 0.05, significant if P < 0.05 or less, and highly significant if P ≤ 0.01.

4. Results

In Table 1 the baseline characteristics of the study groups are shown. The mean age of controls and diabetic cases were 50 ± 4.29 years and 54 ± 6.12 years respectively with insignificant p-value (=0.89). However, the majority of them (48%) were in the age group of 45-65 years. Both the groups were also gender-wise matched. The mean BMI of diabetic subjects (25.9±3.29 kg/m2) was observed to be higher than that of the non-diabetic control group (23.72±2.99 kg/m2) but it was not statistically significant as the p-value was < 0.061. Mean waist circumference in diabetic females was significantly higher than that of the control group (86.34±2.68 vs75.63 ±1.65 cm), p-value <0.001. The waist circumference of the diabetic male group was also higher than control males (89.56±3.39 cm vs 85.67±2.92cm; p<0.001. The normal waist-hip ratio in males is <0.90 and females is < 0.85). Among the studied subjects 26 diabetic males had increased WHR whereas 22 diabetic females had WHR > 0.85. In the control group, WHR was within normal limits.

Table 2 illustrates the levels of serum leptin levels and other biochemical parameters in the diabetic and healthy control groups. Fasting blood glucose was found to be significantly raised in the diabetic group than healthy group (160.57 ± 48.82mg/dl and 93.83± 11.47mg/dl; p< 0.001). The meanGlycated hemoglobin (HbA1c) level in the diabetic group was raised (8.01±2.09%) while in non-diabetics it was within normal limits (5.30 ±0.72%). Serum triglycerides were significantly increased (p< 0.001) whereas HDL-C (p< 0.001) was significantly reduced in diabetic cases than in healthy controls. Total cholesterol and LDL-C levels were observed to be higher in diabetics, however, the difference was not statistically significant. In the present study the fasting serum insulin and HOMA-IR parameters were significantly higher in diabetic subjects (27.89 ±5.99 μIU/L, 9.84 ±5.45) than in healthy control (16.91 ±8.92 μIU/L, 3.42 ±1.12) groups. Of the total 100 study subjects the mean ± SD leptin concentration was 19.75±6.57 ng/ml. Mean serum levels of leptin in diabetic cases were 26.83± 7.63 ng/ml was significantly raised (p<0.001) than 12.64 ±2.81 ng/ml of the control group. Serum levels of leptin in diabetic females cases were 30.84 ± 15.98 ng/ml and were found to be significantly raised (p< 0.001)as compared to that of the healthy female control group(13.84±5.42 ng/ml). The serum leptin levels in diabetic males were 22.98±10.71 ng/ml and those in healthy control male was 5.46±2.15 ng/ml. This difference was highly statistically significant (p< 0.001). The mean ±SD serum leptin levels of diabetic females (30.84±15.98 ng/ml) were found to be significantly higher than diabetic males (22.98±10.71 ng/ml) with p<0.001.

Table 3 depicts the correlation of serum leptin levels with other biochemical tests in study subjects. In this study, we observed a significant positive correlation of serum leptin with fasting glucose (r=0.426,p < 0.0001), BMI (r=0.341,p<0.05), and WC (r=0.482,p, <0.001). And WHR (r=0.216,p<0.001)in study subjects with a stronger coefficient of correlation in diabetic cases than in healthy controls. However, HDL-C levels were significantly negatively (r= -0.02,p=0.029) correlated with serum leptin in both study groups. There was a significant positive correlation of serum leptin with HOMA-IR (r=0.346,p<0.001) in diabetic cases while no correlation was seen in healthy controls.

5. Discussion

In the present study conducted in the population of the KumaunUttarakhandwith previous studies explaining high leptin levels may be partly contributed by the increased body fat percentage calculated by waist circumference, an indicator of abdominal obesity.[21–23] Jiaojiao Huang in their study observed the association of elevated leptin levels in centrally obese Chinese subjects with T2DM.[24] Kurajoh M et alrisk, as well as the presence of microvascular complications and cardiac autonomic dysfunction in T2DM patients.[25–27]

The levels of leptin were significantly higher in females than in males of the study groups. However, both the study groups were age and gender-matched. This observation further supports the earlier studies demonstrating that females have more subcutaneous fat which expresses more leptin mRNA than visceral fat. In addition, evidence suggests there exists a negative correlation between leptin

Table 1: Baseline characteristics of the study populations

Age (years)	Healthy Controls (n=50)	Diabetic Subjects (n=50)
20-35	08 (16%)	4(8%)
36-45	11 (22%)	12(24%)
46-55	09 (18%)	18((36%)
56-65	12 (24%)	09(18%)
>65	10(20%)	07(14%)
Mean age	50±4.29	54±6.12
Males	29	32*
Females	21	18*
BMI(kg/m2)	23.72±2.99	24.9±3.29**
WC(cm)		
Female	75.63 ±1.65	86.34±2.68***
Male	85.67 ± 2.92	89.56±3.39***
WHR		
Females <0.85	21	26**
Males >0.90	18	22**

*p>0.05, **p<0.01,***p<0.001BMI(body mass index), WC(waist circumference ,WHR(waist hip ratio)

Table 2: Correlation between serum leptin levels and biochemical parameters among study subjects

Parameters	Healthy Controls		Diabetic subjects	
	r value	p value	r value	p value
Age	0.321	0.042	0.96	0.06
Sex	0.384	0.006	0.52	<0.001
FBS	0.242	< 0.0001	0.426	0.001
BMI	0.162	0.056	0.341	<0.01
WC	0.286	<0.001	0.482	<0.001
WHR	0.121	0.05	0.218	<0.05
HbA1c	0.351	< 0.0.001	0.06	0.025
Total Cholestrol	0.172	0.21	0.18	0.20
Triglyceride	0.472	0.042	0.52	<0.001
LDLc	0.421	0.068	0.56	0.059
HDLc	-0.026	0.015	-0.02	0.029
Insulin	0.31	0.042	0.51	<0.001
HOMA IR	0.36	0.031	0.346	<0.001

Table 3: Comparison of serum leptin concentrations with incidence of dyslipidemias in study subjects

Lipid profile status	Normal serum Leptin		High serum leptin	
	Females (3.7-11.1ng/ml)	Males (2.0-5.6 ng/ml)	Females (>11.1 ng/ml)	Males (<5.6 ng/ml)
Dyslipidemias (n=58)	3	7	16	32
Nomal Lipidprofile (n=42)	15	18	5	4

and testosterone levels,[28] and there is stimulation of leptin mRNA production by 17β-estradiol, which is one of the women's sexual hormones.[29] These differences in fat mass, body fat distribution, and sex hormones may explain the increased leptin levels in women compared with men seen in this study.

In this study, we have observed a highly significant positive correlation between leptin levels and BMI, and WC in study subjects. This finding further supports the existing evidence that circulating leptin levels are directly related to body fat rather than overall obesity and it is the body fat distribution that determines the development of insulin resistance and diabetes mellitus.[22,28,29] Izquierdo AG, et al reported that serum leptin can serve as an indicator of body fat content and its concentration increases exponentially with body fat percentage.[30] Furthermore, Kotsis V et al in a study on the European population concluded that leptin sensitivity can be restored by reducing circulating leptin levels to a physiologically healthy range and it is a viable antiobesity and antidiabetic strategy.[31] In contrast, Liu W et al observed no difference in leptin concentration in newly diagnosed T2DM patients as compared to controls who were matched in age and BMI.[32]

High fasting serum insulin and insulin resistance as HOMA –IR was seen in diabetic patients as compared to healthy controls. We found a significant positive correlation between serum leptin and HOMA-IR in diabetic subjects. Furthermore, a positive relationship was also observed between serum leptin with insulin and BMI in both study groups. Moonishaa TM, et al concluded that leptin is a marker of Insulin Resistance in Type 2 Diabetes Mellitus and there exists a positive interaction between insulin and leptin. In addition, leptin was also found to be linked with body fat percentage, BMI, and insulin concentration.[33] Oleshchok et al in a study on metabolic syndrome patients concluded that hyperleptinemia is a good predictor of insulin resistance syndrome. IR occurs when insulin hormone in its normal levels is not able to impart its effect on its target insulin target organs including the liver, muscle, and adipose tissue resulting in their insufficient glucose uptake.[34] In Jackson Heart Study conducted on African Americans revealed an association between leptin and incident type 2 diabetes mellitus. They found an increased risk of incident type 2 diabetes with increased leptin levels is mediated through insulin resistance and is present only among males and centrally obese subjects.[35] In addition in the Ceddia RB et al study, insulin resistance was a main determinant of leptin levels in obese as well as diabetes patients.[36] Thus it can be suggested that chronic hyperinsulinemia and resistance to insulin actions, a known underlying mechanism of type 2 DM, may have contributed to raised leptin levels (hyperleptinemia), observed in diabetic cases of this study.

Lipid abnormalities in T2DM is a major risk factor for cardiovascular diseases and the ratio of lipids have been shown to predict risk of complications better than individual lipids. Similarly in the present study significantly higher triglyceride /HDLc ratio and LDLc/HDLc ratio in study subjects while no significant alterations were observed in TC and LDLc in diabetic cases as compared to healthy controls. Dyslipidemia based on LDLc /HDLc >3 was observed in 58 % of the subjects studied. Of these 48% were those with high leptin levels. It was found that high serum leptin levels were related to a higher incidence of dyslipidemia, as compared to normal leptin. This result is in agreement with previous studies.[37,38] In the Indian population, Anil et al concluded that higher leptin levels may be considered an additional risk factor in patients of T2DM with obesity and dyslipidemias.[39] Diwan AG et al reported the association of high leptin levels with dyslipidemias in newly diagnosed diabetic subjects.[40] Recently in a multiple community study, serum lipidomics profiles revealed some potential lipid markers for prediabetes and type 2 diabetes patients.[41]

6. Conclusions

To conclude, in this study we have observed significantly high levels of leptin in known diabetic cases matched in BMI but with higher waist circumference and increased waist-hip ratio than the healthy controls. The raised levels of leptin were found to be positively correlated with BMI, WC, insulin resistance, and dyslipidemias in the study groups. Thus the routine check of anthropometric parameters indicating central obesity, lipid profile, and leptin assays in diabetes patients should be encouraged by clinicians. To reduce the diabetes epidemic and its associated complications in India, spreading awareness regarding lifestyle modification and routine health education should be initiated. In the Kumaun

7. Limitations

1. This was a hospital-based study conducted on a small sample size so its results cannot be generalized to the community. However, previous studies with valid conclusions were also conducted on similar or smaller sample sizes.
2. In this study, the diabetes patients were not homologized based on body fat content, use of various anti-diabetic drugs, and duration of disease.

8. Author Contributions

1. Design of Work, analysis.
2. Interpretation of the data.
3. Drafting the work.

9. Conflicts of Interest

None.

10. Source of Funding

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